

Extremely preterm born children at very high risk for developing autism spectrum disorder

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ABSTRACT

This study aimed to provide a more comprehensive picture of the prevalence of autism spectrum disorder (ASD) in a geographic cohort of extremely preterm born adolescents by using established diagnostic instruments in addition to screening instruments. 53 participants passed a screening procedure with two screening instruments and a diagnostic evaluation with a semi-structured assessment and a parent interview. 28% of the adolescents had a community based clinical diagnosis of ASD. When research diagnoses were also taken into account, this rate increased to 40%. Intellectual disability, language impairment and behavioural difficulties are characteristic for these children with ASD. This study is to our knowledge the first to use ASD-specific diagnostic instruments to confirm ASD diagnoses in extremely preterm born children in early adolescence. The study expands findings of previous research and raises the need for follow-up into late childhood and early adolescence.

KEYWORDS

Extremely preterm born children

Late childhood and early adolescence

Screening tools and ASD specific diagnostic measurements

High prevalence of ASD

INTRODUCTION

In the past decades, major advances in perinatal care have increased the survival rate of extremely preterm born children, born before 27 weeks of gestation (1). Follow-up studies have shown that these children are often confronted with developmental problems and psychiatric diagnoses in late childhood and early adolescence (2–9). Studies also suggest a link between extreme prematurity and autism spectrum disorder (ASD), characterised by persistent deficits in social communication and social interaction, and restrictive and repetitive patterns of behaviours, interests or activities (10). Prematurity and low birth weight are considered to be risk factors for ASD (11–17). Two recent studies even found a gradual increased risk of traits of ASD with shorter gestation (18,19). Screening studies in early childhood revealed that features of ASD have a disproportionally higher prevalence in the preterm compared to the general population (20–23). Studies with the Modified-Checklist for Autism in Toddlers (M-CHAT) (24,25) found screening percentages between 21 and 41% (20–22). The use of multiple screening instruments, resulted in comparable percentages (26,27).

Screening in late childhood and early adolescence revealed similar results. Hack and colleagues (2009) (28) examined a group of 8-year-old children (birth weight < 1000 g) and found higher symptom severity scores in these children compared with term peers. In another study, scores on the Autism Spectrum Screening Questionnaire (29) were higher for very preterm adolescents (gestational age < 32 weeks), compared with their term-born counterparts (30).

Since several studies indicated that the high frequency of neurological, cognitive and sensory difficulties may give rise to false-positive screening classifications for ASD (21,22,26,31), a diagnostic evaluation to confirm true rates of ASD is indicated. To our knowledge, only one study confirmed a positive ASD screen with a further assessment in late childhood: of the 15.8% children with a positive screen on the Social Communication

Questionnaire (SCQ) (32), 8% was diagnosed with ASD following a psychiatric evaluation at 11 years (33). However, clinical assessment involving direct observation by a clinician was not performed (26). The only studies that did include a direct observation measure were conducted with infants (2 years; birth weight < 1500 g) (27) and older adolescents (16 - 21 years; birth weight < 2000 g) (34) and resulted in prevalence rates of 13% (27) and 5% (34), respectively.

To conclude, a detailed observation of the prevalence of ASD using both parent report and direct observation is not yet available for the age group between 11 and 16 years. The current study therefore aims to provide a more substantiated picture of ASD prevalence in extremely preterm born children in their early adolescence by using internationally established diagnostic instruments in addition to screening tools. IQ, language, and behavioural characteristics of children with and without ASD are compared.

METHODS

Participants

Participants in this study belonged to the Extremely Preterm Infants in BELgium (EPIBEL) cohort. In this cohort, perinatal data of all the children born before 27 weeks of gestation in a two-year period (1999 and 2000) were collected (35). At 3 years of age, the cognitive and motor development of the Flemish (Dutch-speaking) children ($n = 91$) was assessed (36) with the Bayley Scales of Infant Development – II (37). For the current study, this group was tested again at the age of 11 - 15 years.

All 91 children included in the 3-year follow-up study were eligible. However, five (5%) of the families moved abroad and seven (8%) were excluded because Dutch was not their mother tongue. The remaining 79 families were contacted by the developmental centres who were responsible for the follow-up of the children in the first years of life, because according to the Belgian privacy law, their home addresses were not available to the authors. Of these 79 families, 66 (84%) replied. The other families could not be reached due to changed contact

information (11%) or no response (5%). Of the 66 responding families, 13 (20%) chose not to participate. As such, data of 53 children of the Flemish part of the EPIBEL cohort (67%) were collected.

Participants were 32 (60%) boys and 21 (40%) girls with a mean age of 12.60 years ($SD = 1.03$; range: 11 - 15); mean birth weight was 791.75 g ($SD = 179.08$; range: 400 - 1210). Mean age of mothers at birth was 27.81 years ($SD = 4.18$, range: 20 - 38). Nine children (17%) suffered from cerebellar haemorrhage grade III or IV and three children from cystic leukomalacia (6%). At the age of three, nine children (17%) were diagnosed with a central motor deficit. Currently, eight children showed major motor impairments (e.g., cerebral palsy) and eight suffered from major visual impairment or blindness. Another three children had auditory difficulties. Eighteen children were part of a twin and four children formed a quadruplet.

Birth weight ($t(89) = -.09, p = .930$), gestational age ($U = 933.50, p = .901$), and age of mother at birth ($U = 913.50, p = .582$) were not significantly different between participants and drop-outs ($n = 38$). The percentage of drop-outs with cerebellar haemorrhage grade III or IV ($n = 7, 18\%$) or cystic leukomalacia ($n = 3, 9\%$) did not differ significantly from the percentage in the participating group ($\chi^2(1) = 0.03, p = .859, \chi^2(1) = 0.18, p = .672$). Nine drop-outs were diagnosed with a central motor deficit at the age of three, which is not significantly different from the number in the participating group ($\chi^2(1) = 1.48, p = .223$). The difference in psychomotor developmental index was marginally significant (drop-outs $M = 66.60, SD = 14.76$; participating $M = 74.87, SD = 19.09$; $t(62) = -1.84, p = .070$). However, drop-outs had a significantly lower mental developmental index ($M = 72.29, SD = 17.27$); $t(69) = -2.60, p = .010$) at the age of 3 than participating children ($M = 83.81, SD = 18.86$).

Materials

Two validated questionnaires were used to estimate ASD symptoms. Firstly, the SCQ lifetime version (32), a 40-item parent questionnaire, was used. Total scores were compared with the established cut-off to screen for ASD (i.e., 15). External validity of the SCQ as a first-level screen for ASD in at-risk samples was demonstrated (sensitivity .88 - .96, specificity .72 - .80) (38,39) and sufficient internal validity was also established (40). Also the Social Responsiveness Scale (SRS) (41,42), a 65-item questionnaire, was administered. A total T-score above the established cut-off of 60 indicates mild to severe shortcomings in social functioning, characteristic for children with mild to severe autistic symptomatology. The SRS is characterised by good internal consistency (Cronbach's alpha > .92) (42), good concurrent validity (42,43) and high sensitivity (.90) and specificity (.88) (42). Parents were asked to complete both questionnaires.

The diagnostic evaluation included the Autism Diagnostic Observation Schedule (ADOS) (44) and the Autism Diagnostic Interview-Revised (ADI-R) (45). The ADOS is a semi-structured assessment of communication, social interaction and play. In this study, module 3 was used and ADOS2-algorithms were applied (46). There is significant evidence for sensitivity and specificity for the ADOS in differentiating children with ASD from children with non-spectrum disorders (46). Inter-rater agreement for diagnostic classification ranged from 81% to 93% and internal consistency for all domains and modules ranged from .47 to .94 (44). We aimed to assess the functioning of all participating children with the ADOS.

The ADI-R, a semi-structured interview in which parents are questioned about their child's social and communication development, was administered when children had a community based clinical diagnosis of ASD or when ADOS-scores were above the cut-off for ASD. Test-retest and interrater reliabilities of the ADI-R are excellent (most intraclass correlation coefficients > .90). Internal consistencies of domain scores ranged from .54 to .84.

Concurrent validity was very good and criterion validity was excellent. Discrimination between ASD versus non-ASD subjects is very good (sensitivity 1.00; specificity > .97) (45).

Higher scores on both diagnostic instruments are indicative for more autistic traits. Both ADOS and ADI-R were administered by the first author, who was trained to research reliability. Inter-rater reliability was obtained by scoring of a number of administrations by three other trained researchers (MD, PW and HR).

Intelligence was assessed using an abridged version of the Wechsler Intelligence Scale for Children-III (WISC-III) (47,48). With four subscales (Similarities, Picture Concepts, Block Design, and Vocabulary), an intelligence quotient was obtained ($M = 100$, $SD = 15$). In addition, language development was examined by means of the Dutch version of the Clinical Evaluation of Language Fundamentals (CELF-IV(-NL)) (49,50), a test for evaluation and diagnosis of language difficulties. Testing with four subtests provided us with a core score for language development ($M = 100$, $SD = 15$).

Information about medical and psychological diagnostic and treatment history and scholastic achievement was obtained using a self-designed questionnaire. Parental, teacher and self-ratings of behavioural problems were collected, using the Child Behaviour Checklist (CBCL), the Teacher Report Form (TRF) and the Youth Self Report (YSR) (51). In addition, the Disruptive Behaviour Disorders Rating Scales (52) (VvGK(53)) was used to screen for disruptive behaviour disorders. Higher scores on these questionnaires indicate higher symptom prevalence.

Statistical analyses

Data were analysed using the Statistical Package for the Social Sciences software version 19 (SPSS Inc., Chicago, IL, USA). In the first part of the results section, descriptive analyses (e.g., cross tabulations) were performed to provide information about the ASD clinical diagnosis status, the ASD diagnostic status based on assessment with the diagnostic instruments

and the ASD screening status of the preterm born children. Four groups of children were formed. Children with a community based clinical diagnosis of ASD form the *clinical ASD*-group. Children with a score above the cut-off for ASD on one or both diagnostic instruments (ADOS and/or ADI-R), but without a former community based clinical diagnosis form the *research ASD*-group. The children from these two diagnostic groups are together considered as the *ASD*-group. A third group is defined as the *ASD concern*-group. This group comprises the children with a positive screen for ASD, on one or both screening questionnaires, but without a clinical or research diagnosis of ASD. Children without a screen for or a diagnosis of ASD are considered as children without ASD (*no ASD*-group).

Independent samples t-tests, chi-square analyses and (one-way) ANOVA's were performed to compare developmental characteristics of the different groups of children. Analyses are labelled 'four groups' when children with a community based clinical diagnosis and children with a research diagnosis are considered separately and 'three groups' when they are considered as one group. Bonferonni post-hoc analyses were applied.

For all analyses, the overall significance level was set at .05. Significance levels below .10 were considered marginally significant.

Ethics

This study was approved by the local ethical committee. Both children and parents gave written informed consents.

RESULTS

Suspicion of ASD

Based on the scores on the screening questionnaires and diagnostic measures, the participating children were divided in four groups reflecting a different grade of suspicion of ASD diagnosis. The first group (*clinical ASD*-group) consisted of 15 (28%) children with a community based clinical diagnosis of ASD, received prior to our evaluation. The second group

(*research ASD-group*) consisted of another six (11%) children with a clinical score on one or both diagnostic measures, who never received a clinical diagnosis. Of the total sample, 21 children (40%) thus had a clinical or research diagnosis of ASD. The two groups of children together are considered as the ASD-group. A third group (*ASD concern-group*) comprises the children with a positive screen on the SCQ and/or the SRS ($n = 12$, 23%), but without a clinical diagnosis or a clinical score on one or both diagnostic measures. The remaining 20 children (38%) belonged to the fourth group of children without any suspicion of ASD.

Information about diagnostic status was retrieved from clinical diagnostic reports. In the first group of 15 (28%) children with a community based clinical diagnosis of ASD, received prior to our evaluation, diagnosis was confirmed by a clinical score on the ADOS in nine of these children. The other six children had severe (cognitive and motor) impairments and behavioural difficulties that made an assessment with the ADOS impossible. Assessments with modules 1 or 2 of the ADOS were considered, but it was clear that the children who were unable to be assessed with the module 3, due to insufficient testability or severe intellectual or motor impairments, were also unable to be tested with another module. Complementary to the ADOS, clinical diagnosis was confirmed with the ADI-R in 10 of these 15 children. Two additional children had a subclinical score on the part of the algorithm that measures communication deficits, but scored clinically on the other parts. Two parents were not willing to participate in this part of the study and the interview was not proposed to the parents of one boy, given the severe impairments of their child. The clinical diagnosis of this boy was the only one which was not confirmed by ADOS or ADI-R. The total percentage of confirmed community based clinical diagnoses was thus 26%.

The second group consisted of six (11%) children with a clinical score on one or both diagnostic measures, who never received a clinical diagnosis. Two children had a clinical score on both the ADOS and the ADI-R, three children only had a clinical score on the ADOS, but

not on the ADI-R and one boy had a clinical score on the ADI-R, but was not assessed with the ADOS, due to severe impairments. These children are labelled as children with a research diagnosis of ASD.

A third group of children, which consisted of a substantive part of the children without a clinical or research diagnosis, also warrant our concerns, when considering their positive screen on the SCQ and/or the SRS ($n = 12$, 23%). Ten SRS screens were found and on the SCQ, parents of five children reported a score above the threshold for ASD.

The remaining 20 children (38%) belonged to the fourth group of children without any suspicion of ASD.

The screening results of the total clinically evaluated group and the different subgroups are shown in Table 1. As depicted, the children in the *clinical ASD*-group all screened positive on at least one of both screeners. In the *research ASD*-group, the results are less clear. Four children screened positive on the SRS, but only two children had a positive screen on the SCQ. Significant differences were found between the children with a clinical diagnosis and a research diagnosis when considering total T-scores on the SRS ($t(19) = 2.63$, $p = .017$) but not the SCQ ($t(18) = 1.83$, $p = .085$). ADOS and ADI-R scores are also presented in Table 1. Children with a clinical or research diagnosis of ASD were more likely to be male ($\chi^2(1, n = 53) = 6.12$, $p = .013$). Of those children diagnosed with ASD, 17 were boys (81%) and 4 were girls (19%). However, no significant gender differences were found for scores on the screening instruments (SCQ $t(43) = 1.16$, $p = .251$; SRS $t(45) = 0.46$, $p = .650$).

Insert Table 1 about here

Intelligence, Language Development and Scholastic Achievement

One sample t-tests revealed that the total group of assessed preterm born children scored significantly below population average ($M = 100$, $SD = 15$) for intelligence ($M = 80.74$, $SD = 18.49$; $t(46) = -7.13$, $p < .001$) and language development ($M = 88.92$, $SD = 19.71$, $t(48) = -$

3.94, $p = .001$). Children who were not able to complete the test ($n = 3$) were assigned the minimum score (being 50 for the WISC-III, and 55 for the CELF-IV-NL) on both tests for these analyses. When the children who were not able to complete the intelligence and the language tests (*clinical ASD-group* $n = 2$, *research ASD-group* $n = 1$) were excluded, very similar results were obtained.

Two one-way ANOVA's showed that the groups of children with or without a positive screen or a research or clinical diagnosis of ASD differed significantly in their level of intelligence (Table 2; $F(2,44) = 5.84$, $p = .006$; $F(3,43) = 4.45$, $p = .008$). Bonferonni post hoc analyses revealed that the *clinical ASD-group* separately ($p = .005$) and the total *ASD-group* ($p = .005$) differed significantly from the *no ASD-group*. Of the children in the *ASD-group*, 47% had an intellectual disability (WISC-III score < 70).

A significant difference was also found for language development (Table 2; $F(2,45) = 4.55$, $p = .016$; $F(3,45) = 4.71$, $p = .006$). The *no ASD-group* scored significantly higher than both the *ASD concern-group* ($p = .044$) and the total *ASD-group* ($p = .025$). The *clinical ASD-group* separately also scored significantly lower ($p = .009$) than the *no ASD-group*. Over 50% of the children in the total *ASD-group* had language difficulties, as did 64% of the children in the *ASD concern-group* (CELF-IV-NL score < 85). Children with a clinical diagnosis did not differ from children with a research diagnosis in intelligence level ($p = 1.000$) and language level ($p = .371$).

Insert Table 2 about here

The percentage of children in special education was higher in the *ASD-group* and in the *ASD concern-group* than in the *no ASD-group* [*ASD* 67%, *ASD concern* 67%, *no ASD* 30%; $\chi^2(2) = 6.72$, $p = .035$].

Behavioural Characteristics

Mean T-scores on the different scales of the Achenbach questionnaires (CBCL $n = 45$, TRF $n = 31$, and YSR $n = 40$) can be found in Table 3. Analyses revealed a significantly higher level of behavioural difficulties in children in the total *ASD*-group, in comparison with the *no ASD*-group. Mainly children from the *clinical ASD*-group showed elevated T-scores (Bonferroni post-hoc analyses). Compared to the *no ASD*-group, significantly more children in the *clinical ASD*-group scored above the clinical cut-off of the CBCL internalizing scale ($\chi^2(1) = 10.76$, $p = .005$), the CBCL externalizing scale ($\chi^2(1) = 6.61$, $p = .037$), the CBCL total problem scale ($\chi^2(1) = 16.13$, $p < .001$), the TRF internalizing scale ($\chi^2(1) = 6.12$, $p = .047$) and the YSR total problem scale ($\chi^2(1) = 6.72$, $p = .035$). Significantly more children of the *ASD concern*-group scored above the clinical cut-off of the CBCL total problem scale ($\chi^2(1) = 7.78$, $p = .021$) compared to the *no ASD*-group.

Insert Table 3 about here

Similar results can be found for behavioural disorder symptoms ($n = 47$). Analyses revealed a higher level of attention deficits, hyperactivity/impulsivity, oppositional defiant disorder problems and conduct disorders symptoms in children with a clinical diagnosis of ASD (please see Table 4).

Insert Table 4 about here

DISCUSSION

This follow-up study expands findings of previous research that demonstrated elevated scores on ASD screeners in preterm born children. In this Flemish cohort of children born before 27 weeks of gestation, the prevalence of community based clinical and/or research diagnoses of ASD was found to be 40%. When only taking into account community based clinical diagnoses made before our evaluation, which were confirmed with a clinical score on the ADOS and/or the ADI-R, and thus applying a stricter rule to estimate the prevalence rate,

the percentage of ASD diagnoses was still 26%. If we would assume that none of the drop-outs has a clinical diagnosis of ASD, which is very unlikely, the prevalence rate in the total Flemish EPIBEL group would still be 16%.

This study is to our knowledge the first to use ASD-specific diagnostic instruments to confirm ASD diagnoses in early adolescence. We made use of two well-validated instruments which are considered the gold standard in the diagnostic process for ASD, namely the ADOS and the ADI-R. They are considered to be the instruments with the highest specificity and sensitivity in the diagnostic assessment for ASD (54). Use of both instruments and the inclusion of clinical diagnostic information, resulted in an extensive coverage of the ASD prevalence in this at-risk group.

This high prevalence rate is remarkable and it obviously exceeds prevalence rates in the general population (55) and in other studies that did not use ASD specific instruments. The prevalence rates are also considerably higher than those reported in the EPICure study, which found a prevalence rate of 8%, based on assessment with a general diagnostic parent interview (33).

In addition to the children with a diagnosis of ASD, our study also discovered a significant rate of elevated scores on both screening instruments. Parents rated clinically significant social-communicative difficulties in an additional 23% of the children. Especially the rate of impairments in social responsiveness, based on data collected with the SRS, is notable. These screening results confirm findings of previous research, in which diagnosed ASD was considered to be the extreme end of a distribution of symptoms that are generally increased in extremely preterm born children (33). These numbers also point out again the importance of the use of diagnostic instruments in research as well as in the clinical field.

Extremely preterm born boys were more likely to be diagnosed with ASD than girls. However, the sex ratio in the ASD groups in this study was only 2.79:1. Moreover, no gender

differences were found for screening results. Children with ASD were also characterised by a lower IQ. Not only were their IQ scores significantly below the mean intelligence score of the children without any suspicion of ASD, almost half of the children with a diagnosis of ASD were intellectually disabled. These results are in line with results of prevalence studies that reported average intelligence in 16 - 56% of all ASD cases (55). In addition, impaired language development was also characteristic. Language problems were however not only detected in children with a diagnosis of ASD but also in other children who screened positive for ASD. Moreover, applying basal scores for both intelligence and language measurements (being 50 for the WISC-III, and 55 for the CELF-IV-NL) to estimate the intelligence level and language development of the children who could not be tested with the instruments we used, may have inflated the mean intelligence and language level of the participating children in both the *clinical* and the *research* ASD-groups, suggesting that the current number may still be an overestimation of their overall cognitive and language capacities. However, omitting these children from the analyses would have overestimated the overall language and cognitive levels even more.

Data also revealed that parents, teachers and the children themselves with a community based clinical diagnosis of ASD reported a significantly higher prevalence of internalizing and externalizing problems than those of children without any suspicion of ASD. A higher rate of disruptive behaviour disorder symptoms was also pinpointed. These results are comparable with results of full term born children with ASD, in which the majority of parents report their child with ASD as having internalising or externalising problems (56).

All these findings confirm suggestions from previous studies, in which ASD is thought to represent part of a preterm phenotype (23) which resembles more the pattern seen in children with syndromic ASD (21) and thought to have a different pathogenic pathway involving global impairment in brain development (33).

This study contributes also in other ways to the research field in this area. Firstly, population studies focusing only on children born before 27 weeks of gestation are scarce. This group of children with an extremely low gestational age made its appearance only in some studies, with the EPICure study as the main example. However, caution in applying the evidence to the development of recently born extremely preterm children is warranted, since medical and neonatal intensive care have developed in the past decade. Moreover, this was only the second study to investigate the prevalence of ASD in late childhood and early adolescence. Most ASD studies in preterm born children were conducted in infancy, a period of childhood in which under- or overestimation of the prevalence of ASD cannot be ruled out. To our knowledge, this was also the first study to include the SRS to screen for ASD symptomatology in extremely preterm born children and this instrument seems to cover a great deal of the difficulties experienced by ex-preterm born children.

Nevertheless some limitations need to be acknowledged. Although we succeeded in reaching 58% of the children of a complete birth cohort (67% of the children who qualified for participation) in an area (Flanders) with a population of more than 6 million inhabitants, the number of participants is still modest. Generalizing the results to the entire EPIBEL-cohort thus needs caution. However, when comparing developmental characteristics of participating and non-participating children, a significantly lower mental developmental index at the age of 3 was found in the non-participating children. Given the strong association that was found between intelligence and diagnostic status of ASD, this finding could suggest an underestimation of the prevalence of ASD in this extremely preterm born cohort. On the other hand, we should acknowledge the possible increased participation of parents of children with a known ASD or with concerns considering the atypical social communicative development of their child. However, the study was not announced as focusing on ASD, but as a general developmental assessment. Secondly, we were not able to assess all children with both the ADOS and the ADI-

R because not all the families were willing to take part in both parts of the research. Moreover, several children had severe impairments which made an assessment with the ADOS impossible. In addition, although we compared the results within the extremely preterm born sample with norm scores and prevalence rates in the general population, not including a full term control sample to compare with the preterm results, limits the robustness of the findings. Lastly, the high rate of twins in the assessed sample may have influenced the results. However, the prevalence of ASD in singletons was somewhat higher, but comparable. Mean intelligence and language scores were similar when twins were excluded.

SUMMARY

This study aimed to provide a more comprehensive picture of the prevalence of autism spectrum disorder (ASD) in a geographic cohort of extremely preterm born children in late childhood and early adolescence by using established ASD-specific diagnostic instruments in addition to screening instruments. 53 children passed a screening procedure with two screening instruments (SCQ and SRS) and a diagnostic evaluation with a semi-structured assessment (ADOS) and a parent interview (ADI-R). 28% of the adolescents had a community based clinical diagnosis of ASD. When research diagnoses were also taken into account, this rate increased to 40%. Intellectual disability, language impairment, and behavioural difficulties are characteristic for these children with ASD. The study confirms and further documents the elevated risk for ASD symptomatology and diagnosis in extremely preterm born children. The high prevalence rate in late childhood and early adolescence that exceeds previously reported rates, raises the need for early screening and diagnostic follow-up during the first years of life to improve opportunities for extremely preterm born children to benefit from early intervention. It also raises the need for follow-up into late childhood and early adolescence, considering the suspected age-related increase in prevalence rates.

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TABLES

Table 1. Total scores on the SRS, the SCQ and mean ADOS and ADI-R scores

Table 1

Total scores on the SRS, the SCQ and mean ADOS and ADI-R scores

SRS					SCQ				ADOS				ADI-R			
	<i>n</i>	Total T-score	Range	% screens	<i>n</i>	Total score	Range	% screens	<i>n</i>	Social Affect	Restricted repetitive behaviours	Total score	<i>n</i>	Reciprocal Social Interaction	Communication	Restricted repetitive behaviours
Total	47	72.2	37 - 123	62%	45	11.3	0 - 30	33%	43	3.2	1.0	4.1				
ASD-group	21	90.0 ¹	47 - 123	90%	20	16.5 ¹	0 - 30	50%	14	7.4 ¹	1.79 ²	9.2 ¹	18	16.4	10.9	5.1
Clinical ASD	15	96.5 ¹	68 - 123	100%	14	18.9 ¹	7 - 30	57%	9	6.4 ¹	2.2 ¹	8.7 ¹	12	18.7	12.5	6.2
Research ASD	6	73.7 ¹	47 - 108	67%	6	10.7	0 - 28	33%	5	9.2 ¹	1.0	10.2 ¹	6	11.6	7.8	3.0
ASD concern	12	71.8 ¹	58 - 98	83%	11	13.2 ²	1 - 25	45%	11	1.3	0.8	2.1				
No ASD	14	45.9	37 - 55	0%	14	2.6	0 - 14	0%	18	1.0	0.4	1.4				
Three groups	$F(2,44) = 34.25, p < .001$				$F(2,42) = 13.43, p < .001$				$F(2,40)$	32.38, = $p < .001$	6.54, $p = .003$	53.29, $p < .001$				
Four groups	$F(3,43) = 32.23, p < .001$				$F(3,41) = 11.57, p < .001$				$F(3,39)$	25.02, = $p < .001$	6.34, $p = .001$	36.49, $p < .001$				

SRS Social Responsiveness Scale (41) ; *SCQ* Social communication Questionnaire (32) ; *ADOS* Autism Diagnostic Observation Schedule (44) ; *ADI-R* Autism Diagnostic Interview-Revised (45) ; *ASD* autism spectrum disorder; *ASD-group* children with a clinical or research diagnosis of autism spectrum disorder; *ASD concern* children with one or two positive screens for autism spectrum disorder; *no ASD-group* children without a clinical or research diagnosis of ASD or positive screen for ASD; ¹significantly different ($p < .001$) from *no ASD-group*, based on post hoc Bonferonni tests; ²significantly different ($p < .01$) from *no ASD-group*, based on post hoc Bonferonni tests; ³significantly different ($p < .05$) from *no ASD-group*, based on post hoc Bonferonni tests

Table 2. Intelligence and language in children with a different grade of suspicion of ASD

Table 2

Intelligence and language in children with a different grade of suspicion of ASD

	<i>WISC-III</i>			<i>CELF-IV-NL</i>		
	<i>n</i>	<i>M</i>	Range	<i>n</i>	<i>M</i>	Range
<i>Total</i>	47	80.7	42 - 113	48	88.9	55 - 124
<i>ASD-group</i>	19	72.5 ²	42 - 105	19	82.8 ³	55 - 124
<i>Clinical ASD</i>	13	69.3 ²	42 - 105	13	77.5 ²	55 - 106
<i>Research ASD</i>	6	79.5	50 - 103	6	94.3	55 - 124
<i>ASD concern</i>	11	78.4	61 - 97	11	81.6 ³	62 - 106
<i>No ASD-group</i>	17	91.5	65 - 113	19	99.2	71 - 121
Three groups	$F(2,44) = 5.84, p = .006$			$F(2,46) = 4.94, p = .011$		
Four groups	$F(3,43) = 4.45, p = .008$			$F(3,45) = 4.71, p = .006$		

WISC-III Wechsler Intelligence Scale for Children – *III* (47,48); *CELF-IV-NL* Clinical Evaluation of Language Fundamentals (49,50); *ASD* autism spectrum disorder; *ASD-group* children with a clinical or research diagnosis of autism spectrum disorder; *ASD concern* children with one or two positive screens for autism spectrum disorder; *no ASD-group* children without a clinical or research diagnosis of or positive screen for autism spectrum disorder; ¹significantly different ($p < .001$) from *no ASD-group*, based on post hoc Bonferonni tests; ²significantly different ($p < .01$) from *no ASD-group*, based on post hoc Bonferonni tests; ³significantly different ($p < .05$) from *no ASD-group*, based on post hoc Bonferonni tests

Table 3. Mean total scale T-scores and percentage of children scoring above the clinical cut-off score (i.e., 70) on the CBCL, TRF and YSR

Table 3

Mean total scale T-scores and percentage of children scoring above the clinical cut-off score (i.e., 70) on the CBCL, TRF and YSR

CBCL					TRF				YSR			
	<i>n</i>	Internalizing	Externalizing	Total	<i>n</i>	Internalizing	Externalizing	Total	<i>n</i>	Internalizing	Externalizing	Total
Total group	45	57.8 (36%)	51.0 (16%)	55.7 (33%)	31	57.8 (32%)	51.0 (16%)	55.7 (19%)	40	51.5 (15%)	43.8 (5%)	46.9 (8%)
<i>ASD-group</i>	19	61.6 ¹ (53%)	55.7 ¹ (20%)	62.2 ¹ (53%)	13	65.0 ² (54%)	56.5 ³ (31%)	63.0 ² (38%)	15	55.5 ³ (27%)	49.7 ² (13%)	54.6 ² (20%)
Clinical <i>ASD</i>	13	65.3 ¹ (62%)	60.2 ¹ (31%)	66.5 ¹ (69%)	8	68.0 ² (63%)	59.5 ³ (38%)	64.8 ² (50%)	10	56.9 ³ (30%)	53.2 ¹ (20%)	58.5 ² (30%)
Research <i>ASD</i>	6	53.5 (33%)	46.0 (0%)	53.0 (17%)	5	60.2 (40%)	51.8 (20%)	60.2 (20%)	5	52.8 (20%)	42.8 (0%)	46.8 (0%)
<i>ASD concern</i>	12	61.4 ² (42%)	53.5 ² (25%)	59.6 ¹ (42%)	8	54.9 (25%)	47.3 (0%)	52.3 (0%)	11	52.0 (18%)	41.4 (0%)	43.1 (0%)
<i>No ASD-group</i>	14	46.7 (7%)	41.0 (0%)	43.3 (0%)	10	50.8 (10%)	46.8 (10%)	49.2 (10%)	14	46.8 (0%)	39.4 (0%)	41.9 (0%)
Three groups	<i>F</i> (2,42) = <i>p</i> < .001	9.58, <i>p</i> < .001	9.48, <i>p</i> < .001	14.79, <i>p</i> < .001	<i>F</i> (2,28) = <i>p</i> = .003	7.09, <i>p</i> = .003	4.27, <i>p</i> = .024	8.69, <i>p</i> = .001	<i>F</i> (2,37) = <i>p</i> = .027	3.97, <i>p</i> = .027	5.88, <i>p</i> = .006	6.10, <i>p</i> = .005
Four groups	<i>F</i> (3,41) = <i>p</i> < .001	9.07, <i>p</i> < .001	11.04, <i>p</i> < .001	14.29, <i>p</i> < .001	<i>F</i> (3,27) = <i>p</i> = .004	5.69, <i>p</i> = .004	3.78, <i>p</i> = .022	6.08, <i>p</i> = .003	<i>F</i> (3,36) = <i>p</i> = .048	2.91, <i>p</i> = .048	6.21, <i>p</i> = .002	5.87, <i>p</i> = .002

CBCL Child Behaviour Checklist (51); *TRF* Teacher Report Form (51); *YSR* Youth Self Report (51); *ASD-group* children with a clinical or research diagnosis of autism spectrum disorder; *ASD concern* children with one or two positive screens for autism spectrum disorder; *no ASD-group* children without a clinical or research diagnosis of or positive screen for autism spectrum disorder; ¹significantly different ($p < .001$) from *no ASD-group*, based on post hoc Bonferonni tests; ²significantly different ($p < .01$) from *no ASD-group*, based on post hoc Bonferonni tests; ³significantly different ($p < .05$) from *no ASD-group*, based on post hoc Bonferonni tests

Table 4. Mean scores on the VvGK

Table 4

Mean scores on the VvGK

		Attention deficits	Hyperactivity/ Impulsivity	Oppositional Defiant Disorder	Conduct Disorder
	<i>n</i> =	<i>M (SD)</i>			
Total group	47	12.3	12.0	12.2	11.7
ASD-group	21	13.5 ¹	13.1 ¹	13.5 ¹	12.4 ³
Clinical ASD	15	13.6 ²	13.7 ¹	13.9 ¹	12.7 ³
Research ASD	6	13.0	11.5	12.7	11.8
ASD concern	12	12.2	12.3 ³	12.3	11.8
No ASD-group	14	10.8	10.1	10.1	10.5
Three groups	<i>F</i> (2,44)	7.28, <i>p</i> = .002	10.58, <i>p</i> < .001	8.69, <i>p</i> = .001	4.07, <i>p</i> = .024
Four groups	<i>F</i> (3,43)	4.94, <i>p</i> = .005	10.09, <i>p</i> < .001	6.18, <i>p</i> = .001	2.96, <i>p</i> = .043

ASD-group children with a clinical or research diagnosis of ASD; ASD concern children with one or two positive screens for ASD; no ASD-group children without a clinical or research diagnosis of or positive screen for ASD; VvGK Vragenlijst voor Gedragsproblemen bij Kinderen (53); ¹significantly different ($p < .001$) from no ASD-group, based on post hoc Bonferonni tests; ²significantly different ($p < .01$) from no ASD-group, based on post hoc Bonferonni tests; ³significantly different ($p < .05$) from no ASD-group, based on post hoc Bonferonni tests